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TITLE: Effectiveness of Acupuncture in the Treatment of Gulf War Illness

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| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT The goals of the DOD funded research, GW080059, have been accomplished. We were successful with our aggressive marketing and advertising efforts in the area of subject recruitment and enrollment. Subject contact, enrollment, data collection and entry are completed. Our preliminary analyses found statistical and clinical significant improvement in our main outcome (the physical component of the Sf-36); that is we found support that individualized acupuncture treatments can reduce the symptoms of at least some veterans with Gulf War Illness. | | | | | |
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INTRODUCTION: This project is a single-blind randomized controlled clinical trial with a wait list control evaluating the effectiveness of individualized acupuncture treatment on subjects' overall health and disease burden. This three and a half-year project compared weekly to biweekly doses of acupuncture. One study arm received biweekly acupuncture for 6 months with measurement collection every two months. The wait list group waited for two months and then received acupuncture once a week for four months with measurement collection every two months. Our primary outcome is the physical functioning subscale of the quality of life scale the SF-36.

BODY: In an effort to better understand this disease and its treatment we gathered additional data for secondary data analyses including the psychosocial variables (depression, anxiety, mood), fatigue, sleep quality, and pain. All of the measurement instruments used in this trial have been used before and published on in peer reviewed scientific journals. All have shown good validity and reliability. Our objectives are to find a successful treatment of GWI, by gathering data to better understand: 1) the effectiveness of acupuncture in treating GWI, 2) the mechanisms of how GWI may be helped by acupuncture.

The original award supported a three year project, but we requested and were awarded supplemental funds and an extension due to challenges of recruitment. This last 6 months of additional funding allowed us to focus on reaching our recruitment goal which had been extended through June 2012, supply treatments, collect measurements, and conduct the primary analysis of the main outcome.

Recruitment efforts this year were aggressive and successful with the continued use of the Manpower database; a federal database of all past and present military employees. We completed eight mass mailings this year; these mailing yielded the most positive results thus far. These initial mailing were followed-up with a postcard reminder to the addresses that were still correct (we did not send postcards to residences for which the post office returned our original letter as "bad address"). We also modified

our protocol and received IRB approval to call veterans on the Manpower database. Further our study medical screening physician extended his appointment slots to meet this final recruitment push.

In order to facilitate veterans' receipt of treatments we hired and trained acupuncturists around the state of Massachusetts and New Hampshire to provide treatments close to where the veterans work and live. Recruitment and training for additional study practitioners continued this year to ensure that study participants have convenient access to practitioners. The addition of these practitioners decreased travel time requirements for study subjects. In addition to the nine practitioners we had trained as a group before treatments began, nine additional practitioners were oriented in July 2011, four additional practitioners were oriented in August 2011 and three were oriented in October 2011. Six more were oriented individually in 2012 as we further honed where to find pockets of eligible participants. The practitioner training materials included a history of the Gulf War, hypothesized causes for the symptoms of Gulf War Illness, the study rationale and methodology, and the Traditional Chinese Medicine diagnoses related to the symptomatology. This orientation enabled the practitioners to understand the deployment experiences of Gulf War veterans as well as the background and possible causes for the veterans' symptoms. We also explained our data collection procedures and offered examples of some of the testing instruments in order to educate the practitioners of the entire study process.

This past year we continued to reach out to the various news media including a study announcement in Veteran's Today publication (Veterannewsnow.com), the posting of flyers at the Newport Naval Station Family Service Center, and an additional article was posted in the online version of Stars & Stripes under Stripes Central. The Springfield Republican interviewed Dr. Conboy which went to press in May 2012 and a press release was also sent to the Lowell Sun newspaper in June 2012.

We maintained our exposure on the Internet through: 1. the website www.91outcomes.com which posted Dr. Conboy's lecture at the University of Southern California's CIR in LA (which presented study design and the preliminary findings), 2. the National Gulf War Resource Center (www.ngwrc.org), 3. Project New Hope of Massachusetts (www.projectnewhopema.org) who did an interview with Dr. Conboy, 4. Twitter, 5. Mass.gov state agencies for veteran's services (<http://www.mass.gov/veterans/health-and-well-being/supportgroups-researchstudies/researchstudies/study-on-gulf-war-illness.html>), 6. The Environmental Illness

Resource (<http://www.ei-resource.org/news/gulf-war-syndrome-news/acupuncture-may-relieve-symptoms-of-gulf-war-syndrome-according-to-ongoing-research/>).

KEY RESEARCH ACCOMPLISHMENTS:

Dr. Conboy published a manuscript describing the study design in the peer reviewed journal, Contemporary Clinical Trials (Conboy L, St John M, Schnyer. The effectiveness of acupuncture in the treatment of Gulf War Illness. Contemp Clin Trials. 2012; Feb (33):557-62. PMID: 22349455.

Dr Conboy has presented on the study design at: 1)Pacific College of Oriental Medicine-invited talk (presented twice/two years), 2)Five Branches Institute-invited talk (presented twice/two years), 3)New England School of Acupuncture Research Lecture Series, 4)Center for Innovation and research on Veterans and Military Families at the University of Southern California-invited talk, 5)Meeting of the Research Advisory Committee (RAC) on Gulf War Veterans' Illnesses-invited talk (presented twice/two years).

REPORTABLE OUTCOMES:

Subject contact:

Below is a summary of our subject contact to date:

Potential subject phone calls to our study phone line: 202
Individual subjects consenting to initial phone call: 161
Individuals who refused or were ineligible: 59
Individuals with screening still in process: 31
Potential subjects receiving in-person medical screening: 8
Subjects active/enrolled: 104

Preliminary Results:

In previous reports, because we could not yet look at the main outcome, we reported on a few subscales including main and secondary complaints from the MYMOP scale and a single item from the Multidimensional Assessment of Fatigue. Using two tailed Student's t-tests we found statistically significant positive improvements in the severity of veterans' self-reported main ($p<0.01$) and secondary ($p<0.009$) complaints as measured by items on the MYMOP¹, self-reported overall health ($p<0.007$) as measured by a single item on the Sf-36², and fatigue

($p < 0.05$) as measured by a single item on the Multidimensional Assessment of Fatigue³(Figure 1). Patient satisfaction with care and confidence in treatment is also very high (95% rated satisfied and confident).

Unblinded Comparisons:

Now that the study is completed, blinding has been broken and we are free to report on the main outcome; that is the physical component subscale of the SF-36⁴. We judged all Sf-36 comparisons for statistical significance using paired Student's t-tests.

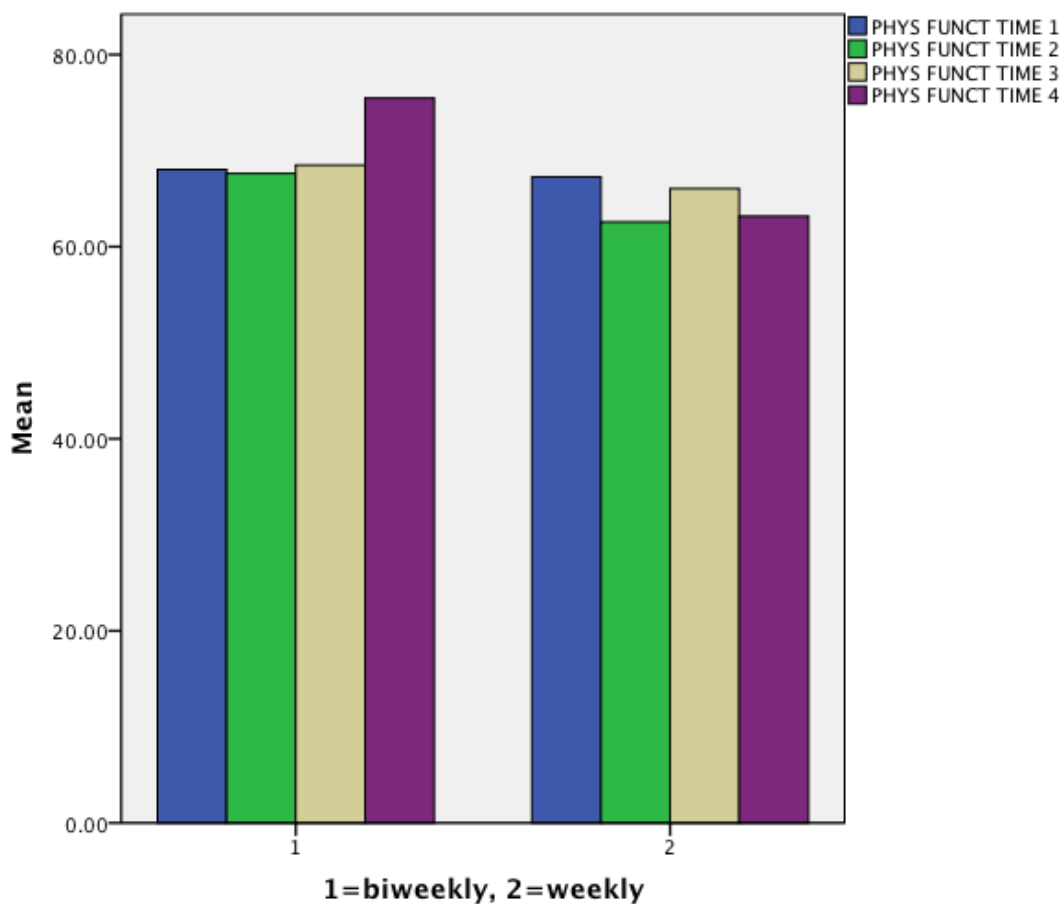
In looking at **Figure 1** (below) it is clear that time on the waitlist is associated with poorer scores for the wait list group. This decrease is statistically significant (MEAN time 1=67.6, MEAN time 2=61.8 $p \leq 0.027$). This decrease in Sf-36 component scores happened while the veterans were waiting for treatment to start and thus this is probably due to veterans' frustration in having to wait for treatment; a number of the veterans mentioned this frustration along with an acknowledgement that they were informed of the necessity for a wait list design and knowledge that they would receive treatment at 2 months. We will explore other changes which occurred during the wait list in later analyses.

Overall, grouping the weekly and biweekly groups together, improvements were statistically significant ($p \leq 0.028$), but **Figure 1** suggests that this result may be led by individuals in the biweekly treatment group. More time on a dose of weekly acupuncture was not associated with statistically significant improvements on this physical component of the Sf-36 for the weekly treatment group overall.

For the biweekly treatment group, scores from time 1 (mean score=68.5) to time 4 (mean score=75.7) did improve with statistical significance $p \leq 0.003$. The same is true if we only consider the shorter time period of time 2 (mean score=65.5) to 4 (mean score=73.7) $p \leq 0.007$. A seven point improvement in this physical component of the Sf-36 is also clinically significant^{5,6,7}. Looking again at **Figure 1** (below), it appears that the biweekly treatment, on average, shows a dramatic effect in this outcome after 6 months of continuous treatment. This result is not merely due to differential dropout; that is the improvement seen from 4 to 6 months is not due to veterans who are healing faster staying with treatment while those that are feeling

benefit dropping out, because no veterans in the biweekly treatment group dropped out of the study between time points three and four.

Figure 1: Physical Functioning Subscale of the SF-36 mean scores for each data collection period by study arm. Time 1 is baseline. Time 2 is after 2 months in the study; time 3 is after 4 months in the study; time 4 is after 6 months in the study. Study group 1 received biweekly acupuncture for 6 months. Study group 2 served as a wait list group for 2 months and then received weekly acupuncture for 4 months. **Higher mean scores indicate better health.**



Other findings will be used for further exploration. For example, the published standard deviation of this subscale is 27.42⁸. Our weekly treatment group showed a similar standard deviation across the four time points (26.8-28.04) while the biweekly group was more stable with standard deviations ranging only up to 24.5. This greater stability suggests that the biweekly regimen may be more consistently helpful for most of the veterans; still weekly treatment may be

enough for some cases and this observation is merely suggestive. We are pursuing additional funding to consider such questions of dose.

Although it is not our main outcome, we also want to report our positive improvements on pain, given the importance of pain treatment for GWI and other veterans. Using the McGill Pain Scale, short form⁹, and pre-post paired Student's t-test we found statistically significant improvements in pain scores comparing Time 2 to time 4 ($p < 0.001$) in the pooled (both treatment groups together) sample with overall sample means moving from a score of 29.9 to 26.5. Our first published outcomes report will look at pain reduction by study arm as well as adherence to protocol (dose).

We also wish to share a few usability outcomes.

Figure 2: Confidence in recommending acupuncture. Subjects showed high levels of confidence in treatment.

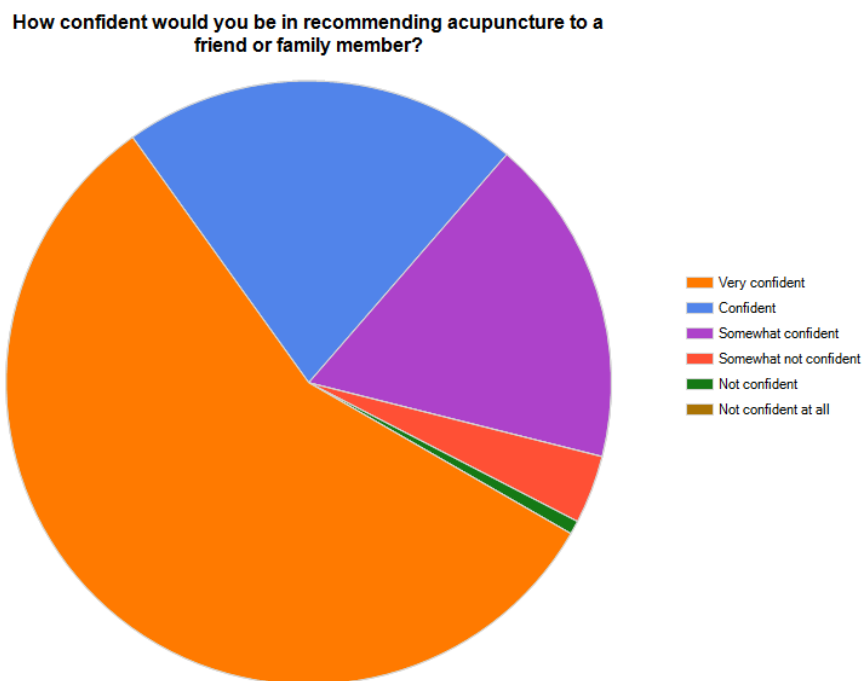
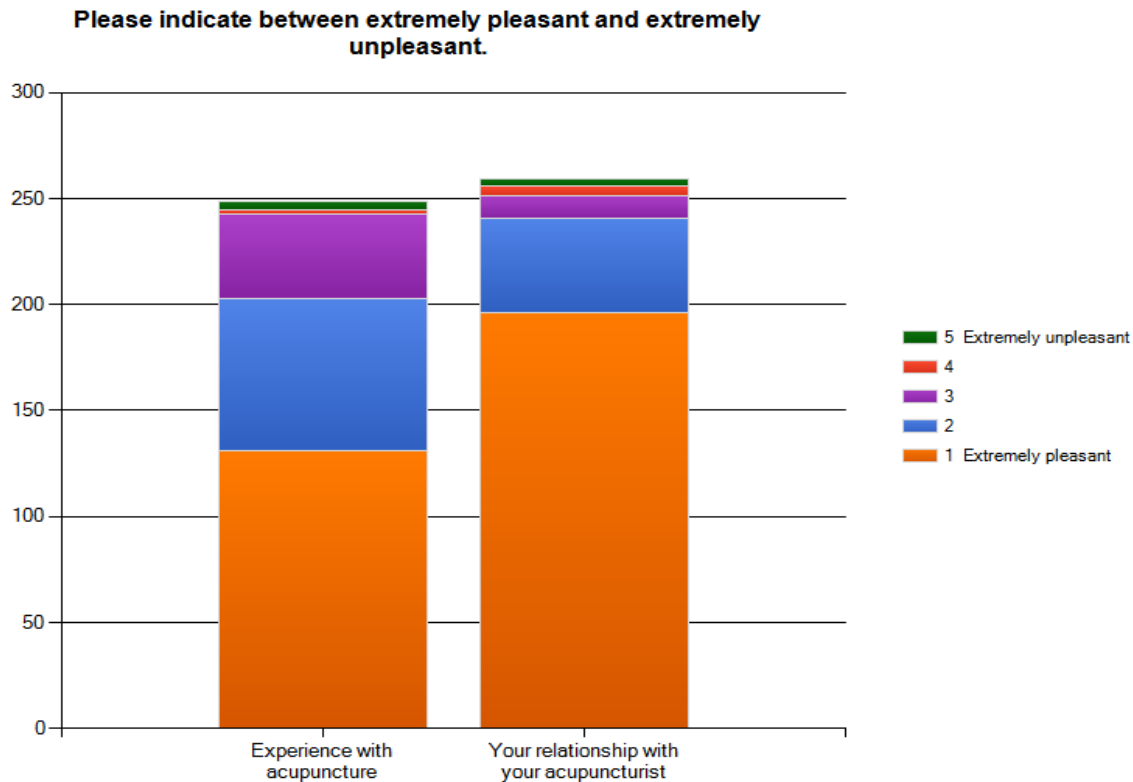


Figure 3: Experience with Acupuncture and the Acupuncturists: Subjects showed high levels of satisfaction with both the acupuncture treatment and the treaters.



Manuscripts and Presentations:

Dr. Conboy and collaborators have published the first manuscript from this study which describes the study design. The citation is below.

Conboy L, St John M, Schnyer R.(2012). The effectiveness of acupuncture in the treatment of Gulf War Illness. Contemp Clin Trials. Feb 10. PMID:22349455.

Dr Conboy will be presenting the preliminary results to at the Society for Acupuncture Research's conference in April 2013.

CONCLUSION:

We have attained a robust study sample, statistical and clinical significance following individualized acupuncture treatments, and excellent reported treatment usability by the sample. We are currently pursuing funding to complete additional analyses to better understand for which veterans acupuncture works best, for which symptoms, and what are the characteristics of the most successful individualized acupuncture treatments. Our goals support the recommendations of the Institute of Medicine's recent report on the treatment of Gulf War Illness which suggests the GWI might be best treated in an individualized way¹⁰. Individualized diagnosis and treatment is the type of acupuncture we offered the veterans and we found good results.

We will mail a public version of these analyses to study subjects as well as the many Army, Veteran Administration, and veteran group members that have helped us with recruitment, and more generally who provided an invaluable education and experience.

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